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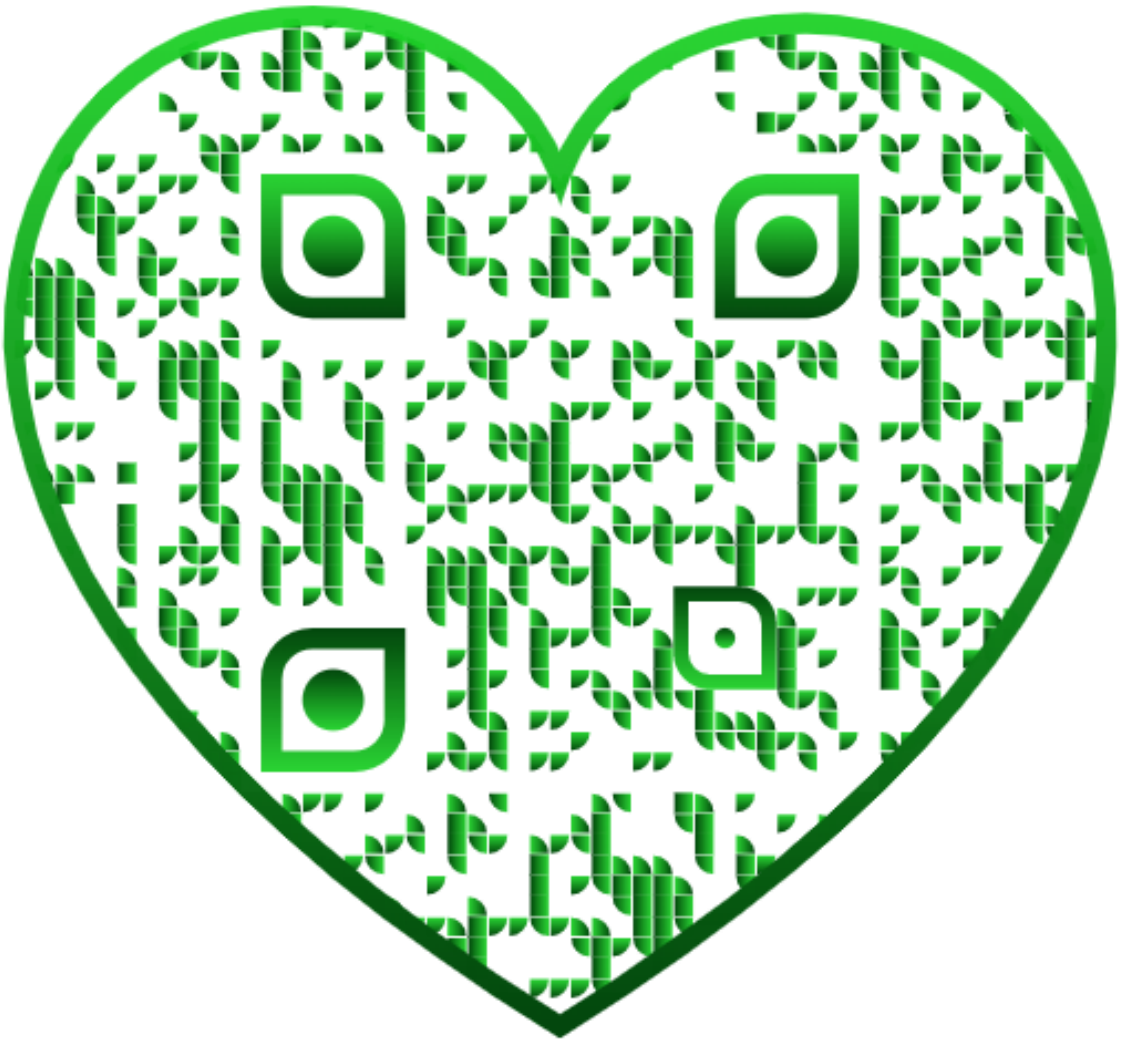
Ministry of Health Malaysia
Pharmaceutical Services Programme

PHARMACIST'S HANDBOOK OF PARENTERAL NUTRITION

In Neonates and Paediatrics

SECOND EDITION

2023



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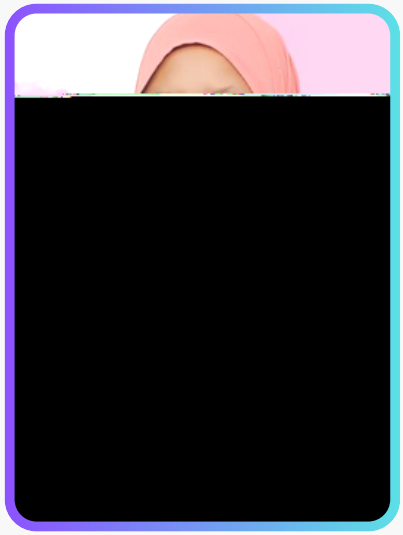
PREFACE



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Parenteral Nutrition (PN) is an essential therapy to correct or prevent nutritional deficiencies when adequate enteral nutrition is not feasible due to impairment or immaturity of gastrointestinal function in neonates and paediatrics. Pharmacists have diverse roles in providing safe and effective PN therapy to optimise clinical outcome in these vulnerable groups of patients.

PN Pharmacy service encompasses both technical and clinical components whereby a holistic patient care is consistently embraced by the pharmacists. The growing need for clinical parenteral nutrition service by pharmacists in ward has extended to cover more disciplines over the past decades. With more recent published evidence on the aspects of PN in paediatrics population, it is an opportune time to develop a second edition of this handbook to ensure practice relevance and excellence.

I sincerely hope that this handbook will serve as a concise guide for pharmacists involved in PN service. It is of utmost importance for the pharmacy fraternity to deliver the best pharmaceutical care to our patients. Lastly, I would like to express my gratitude to everyone who has contributed directly or indirectly to the development of this handbook.

Thank you.

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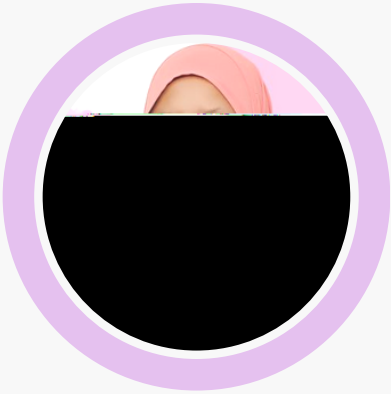

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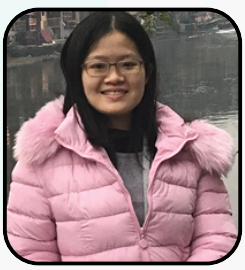

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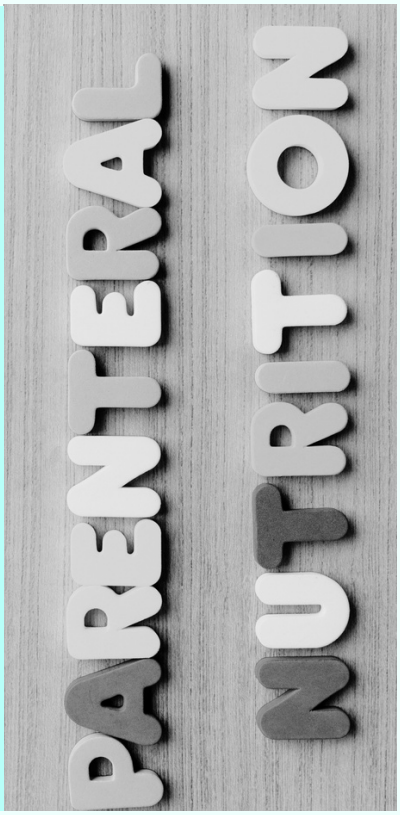

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1.0 Introduction

Provision of parenteral nutrition (PN) in the paediatric population could be challenging due to the wide range of patients, ranging from extremely premature neonates up to obese teenagers. Therefore, it is extremely important to take into account of patient's age and maturity-related changes of the metabolism, fluid and nutrient requirements along with clinical situation in delivering PN regimen. Therefore, the substrate requirements of paediatric patient cannot be proportionally derived from adult requirement but are determined according to age-specific and physiological conditions.[1]

In comparison to older paediatric patients or adults, term and preterm neonates have different energy requirements due to an extremely low body storage of nutrients in many aspects. These include immature gastrointestinal system, high metabolic rates and the tendency to suffer from evaporative fluid losses, thus requiring a carefully monitored intake to suit their specific requirements.[2]

The goals of Parenteral Nutrition (PN) in paediatric patients are to :

- Provide sufficient nutrients to prevent negative energy and nitrogen balance
- Prevent essential fatty acid deficiency
- Support normal rates of growth without increasing significant morbidity

2.0 Indication for Parenteral Nutrition

Essentially, the initiation of PN requires risk benefit assessment and comprehensive clinical judgement.[3] PN is indicated in paediatric patient that cannot be adequately fed or has contraindication for oral or enteral feeding, for instance patient with gastrointestinal diseases such a intestinal failure, malabsorption, short bowel syndrome and more.

For neonates, PN soon after birth should be commenced for [4,5]:

- Preterm neonates < 32 weeks and/or birthweight < 1500 g
- Neonates with high risk of necrotising enterocolitis (NEC)
- Neonates with illness for which establishment of enteral feeding is thought to be delayed for 3-5 days
- Neonates with surgical gastrointestinal tract anomalies
- Neonates who are required to be prolonged nil by mouth due to surgery

3.0 Line Access for Parenteral Nutrition Delivery

In general, PN solution can be administered via central or peripheral vein. The selection of appropriate line access should take into the consideration of the patient's vascular access history, venous anatomy, coagulation status, the anticipated duration of PN, the care setting (hospital versus others) and the nature of the underlying disease.[2] In addition, the ultimate concentration and osmolarity of PN solution also should be reflected in the choice of line access as shown in Table 1.

An infusion pump should be used to infuse all PN solution in order to ensure the efficacy and safe provision of nutrition in neonatal and paediatric patients. PN solution and intravenous lipid emulsion (IVLE) should be administered using photo-protected tubing set and attached with in-line filter. The recommended in-line filters are 0.2 µm filter for aqueous solution and 1.2 µm filter for lipid containing solution.

The osmolarity of PN solution is mainly accounted by the presence of dextrose. Dextrose concentration above 10% is associated with increased risk of phlebitis. If dextrose concentration in PN solution exceeds 12.5%, a central venous catheter or Peripherally Inserted Central Catheter (PICC) line should be used. The amino acid concentration in peripheral veins should not exceed 2.5% as it may increase overall solution osmolarity.[8] The addition of lipid emulsion with amino acid and glucose solution offers additional protection to the peripheral venous endothelium against phlebitis.[9]

Table 1. The differences between central and peripheral venous access for PN delivery[6]

Venous Access	Peripheral Access	Central Access
Duration	• Short term	• Long Term
Sites	• Forearm • Back of the hand	• Internal jugular vein • Subclavian vein • Femoral vein
Types	• Peripheral venous catheter • Midline catheter	• Central venous catheter (CVC) • Peripherally inserted central catheter (PICC) • Umbilical catheter
Osmolarity	• < 900 mOsm/L[7]	• No limit in osmolarity
Advantages	• Easier to place	• Easier to maintain • More durable • Less prone to phlebitis and extravasation
Disadvantages	• Prone to phlebitis and extravasation • Easy to dislodge • Difficult to maintain • May require routine replacement	• Difficult to place • Higher risk of insertion procedure

4.0 Energy Requirements

PN is supplied as an energy fuel to cover nutritional needs of the patient for basal metabolic rate, physical activity, growth and to correct pre-existing malnutrition. Generally, neonates require less calorie when fed parenterally than during enteral feeding because there is no energy lost in stools and there is less thermogenesis. Neonates require greater calories per kg body weight compared to children and adults due to increased cellular growth and physical activity and higher heat loss.

Two methods for calculation of energy requirement in neonates and paediatrics :

1. Schofield's equations

2. Range of calorie requirement based on phases

1. **Schofield's equations**

For calculation of resting energy expenditure (REE), the use of Schofield's equation for weight can be recommended. Total parenteral energy requirements of stable patients can be calculated from REE with adding constants for physical activity, (catch-up) growth and adjusted for disease states that increase or decrease REE.

Table 2. Schofield's equations for calculating REE (kcal/day)

Age	Boys	Girls
0-3 years	59.5 x (weight in kg) - 30	58.3 x (weight in kg) - 31
3-10 years	22.7 x (weight in kg) + 504	20.3 x (weight in kg) + 486
10-18 years	17.7 x (weight in kg) + 658	13.4 x (weight in kg) + 692

Suggestion of metabolic constants (physical activity levels, PALs):

1.0: for sleeping
1.2: for lying awake and for sitting quietly
1.4-1.5: for standing quietly or sitting activities
1.7: reflects a moderate level of activity for healthy children
1.5 and 2.0: are estimates for light and vigorous levels of activity

Most children receiving PN will have low PALs

Children recovering from malnutrition need extra calories to correct their growth deficits i.e. weight and height. Calculation may be based on the actual weight multiplied by 1.2-1.5, or more in severe cases of failure to thrive, although this is rarely the predominant nutritional aim during the period of PN.

2. Range of calorie requirement based on phases

This method of energy requirement calculation is based on the paediatric patient current condition, which are either acute, stable or recovery phase.

Table 3. Energy requirements (kcal/kg/day) for parenteral nutrition in different phases of disease[11]

Age (Years)	2005	2016 Recovery Phase	2016 Stable Phase	2016 Acute Phase
Preterm	110 - 120	90 - 120		45 - 55[a]
0 - 1	90 - 100	75 - 85	60 -65	45 - 50
1- 7	75 - 90	65 - 75	55 - 60	40 - 45
7 - 12	60 - 75	55 - 65	40 - 55	30 - 40
12 - 18	30 - 60	30 - 55	25 - 40	20 - 30

[a]Recommended energy intake during the first day of life.

Phase of illness	Elaboration
Acute	Resuscitation phase when patient require vital organ support (sedation, mechanical ventilation, vasopressor, fluid resuscitation)
Stable	Patient is stable on or can be weaned from this vital support
Recovery	Patient who is mobilising

5.0 Components of PN

Nutrition provided by intravenous formulation consists of fluids, carbohydrates, proteins, fats, electrolytes, vitamins and trace elements. PN can be supplied as:

- Aqueous solution that contains water, proteins, carbohydrates, electrolytes, vitamins and trace elements.
- All in one solution that contains water, carbohydrates, proteins, fats, electrolytes, vitamins and trace elements. All in one solution can be obtained commercially or compounded tailored to the patients' requirements.

5.1 Fluid

Fluids are generally supplied as water that acts as a carrier for nutrients and metabolites. Water and electrolyte requirements per unit body mass are generally very high in neonates and decrease with age until adulthood.

Most of the researches described on the adaptation processes of water and electrolyte metabolism related to the preterm neonates or adults, unfortunately limited information is known of these processes in older children. Most of the recommendations are generally based on extrapolations from data on neonates and adults.

Fluid requirements as shown in tables 4-8 below are for general guideline. Fluids may need to be adjusted specific to patient's clinical condition. For an example, if a patient is suffering from Patent Ductus Arteriosus (PDA), fluids may need to be restricted to prevent worsening of the PDA.

5.1.1. Fluid Requirement in Neonatal Period

Phase I: Transition phase:

- Insensible water loss via immature skin lasting hours to days
- In term neonates, postnatal weight loss occur during 2-5 days and should not exceed 10% of birth weight
- In ELBW and LBW neonates, 7-10% weight loss seems to be adequate
- Gradual increase of fluid intake is recommended in preterm and term neonates after birth
- Goal:
  - -Allow contraction of extracellular fluid (ECF) with negative water and Na balance
  - -Secure a sufficient urinary output without oliguria (< 0.5-1.0 ml/kg/H) for longer than 12 hours
  - -Ensure regulation of body temperature by providing enough fluid

Table 4. Fluid requirement in neonate during transition phase[10]

Fluid requirement (ml/kg/day)					
Day of Life	D1	D2	D3	D4	D5
Term neonate	40-60	50-70	60-80	60-100	100-140
Preterm nenonate >1500g	60-80	80-100	100-120	120-140	140-160
Preterm neonate 1000-1500g	70-90	90-110	110-130	130-150	160-180
Preterm neonate <1000g	80-100	100-120	120-140	140-160	160-180

Phase II: Intermediate phase

- Period between minimal weight (maximal weight loss) and return to birth weight
- Birth weight regained by 7-10 days of life in normal breastfed term neonates
- Goal:
  - -Replete body for electrolyte losses and replace actual water and electrolytes
  - -Maintain proper fluid and electrolyte homeostasis while neonate is regaining birth weight

Table 5. Fluid requirement in neonate during intermediate phase[10]

Fluid requirement (ml/kg/day)	
Term neonate	140-170
Preterm neonate > 1500g	140-160
Preterm neonate < 1500g	140-160

Phase III: Stable growth

- Continuous weight gain with positive net balance for water and electrolyte
- Goal:
  - -Replace losses of water and electrolytes
  - -Provide enough extra water and electrolyte to reach an adequate rate of growth with adequate fluid and electrolyte homeostasis

Table 6. Fluid requirement in neonate during stable growth[10]

Fluid requirement (ml/kg/day)	
Term neonate Preterm neonate > 1500g Preterm neonate < 1500g	140-160

5.1.2. Fluid Requirement in Children and Infant Beyond Neonatal Period

Holliday and Segar formula is employed to calculate the maintenance water needs in children by determining caloric/ water needs.[10]

Table 7. Fluid requirement in children based on weight[10]

Weight	ml/kg/day	ml/kg/H
A. the first 10kg	100	4
B. weight between 10 and 20kg	+50 ml/extra kg/d	+2 ml/extra kg/H
C. weight above 20kg	+25 ml/extra kg/d	+1 ml/extra kg/H
Sum total requirements	A+B+C	A+B+C

Table 8. Fluid requirement in children based on age[10]

Age	<1y	1-2y	3-5y	6-12y	13-18y
Fluid (ml/kg/day)	120-150	80-120	80-100	60-80	50-70

5.2 Carbohydrates

Carbohydrates are one of the major contributors of energy in parenteral nutrition. Ideally, it should constitute 60-75% of the total non-protein calories in the TPN regimen.[4] Dextrose, the monohydrated form of glucose is used in PN solution and each gram of glucose provides 3.4 kcal. However, in general practice, 4 kcal/g glucose is widely used in Malaysia. There is no essential amount of carbohydrate needed because the human body is capable of forming carbohydrates from lipids and amino acids. Nonetheless, its presence is still important to prevent breakdown of somatic protein sources.[9] Moreover, production capacity from endogenous glucose production and gluconeogenesis is limited in preterm neonates, who depend both on exogenous glucose and PN components to maintain glucose homeostasis and avoid hypoglycaemia.

The amount of glucose to be provided by PN should be guided by:

- The balance between meeting energy needs and the risks of overfeeding/excess glucose load
- Phase of illness (acute, stable, recovery/growing)
- Macronutrient supply from enteral and parenteral nutrition
- Glucose administered outside enteral and parenteral nutrition, e.g. with medication.

In extremely preterm neonates (24-29 weeks), endogenous glucose production and gluconeogenesis on day 3-4 are not affected by the glucose infusion rate. In contrast, in moderately preterm neonates (31±1.5 weeks), endogenous glucose production is suppressed completely by parenteral glucose intake. The inability to suppress glucose production or gluconeogenesis may contribute to the risk of hyperglycaemia in extremely preterm neonates, hence excess glucose load needs to be avoided.

Carbohydrate requirements are shown below (Table 9 & 10). It is worth to note that maximum dextrose concentration of the peripheral PN solution is 10-12.5% while for the central PN solution is 25%. However, glucose intake of 10% on day 1 of postnatal life for both preterm and term neonates is commonly practiced in the government hospitals in Malaysia.[22]

Table 9. Recommended parenteral glucose in neonate (< 28 days of life)[8]

Neonate Category	Day 1	Day 2 onwards
	Start with	Increase gradually over 2-3 days to
Preterm	4-8 mg/kg/min (5.8-11.5g/kg/day)	Target 8-10 mg/kg/min (11.5-14.4 g/kg/day) Min 4-12 mg/kg/min (5.8-17.3g/kg/day)
Term	2.5 mg/kg/min (3.6-7.2g/kg/day)	Target 5-10mg/kg/min (7.2-14.4g/kg/day) Min 2.5-12 mg/kg/min (3.6-17.3g/kg/day)

Glucose metabolism is highly modified during critical illness. Glucose intake does not lower protein catabolism in the acute phase of critical illness, and the fact that hyperglycemia occurs frequently during this phase warrants for reduced glucose supply. The decrease in parenteral glucose intake is also in line with the lower energy recommendation in acute phase of critical illness.

Newborns < 28 days of age with an episode of acute illness (e.g. infection or sepsis), should temporarily receive the carbohydrate supply of day 1, guided by blood glucose levels.

Table 10. Recommended parenteral glucose supply in neonates and children according to body weight and phase of illness[8]

Weight	Acute Phase	Stable Phase	Recovery Phase
28 d-10 kg	2-4 mg/kg/min (2.9-5.8 g/kg/day)	4-6 mg/kg/min (5.8-8.6 g/kg/day)	6-10 mg/kg/min (8.6-14 g/kg/day)
11-30 kg	1.5-2.5 mg/kg/min (3.6-2.9 g/kg/day)	2-4 mg/kg/min (2.8-5.8 g/kg/day)	3-6 mg/kg/min (4.3-8.6 g/kg/day)
31-45 kg	1-1.5 mg/kg/min (1.4-2.2 g/kg/day)	1.5-3 mg/kg/min (2.2-4.3 g/kg/day)	3-4 mg/kg/min (4.3-5.8 g/kg/day)
>45 kg	0.5-1 mg/kg/min (0.7-1.4 g/kg/day)	1-2 mg/kg/min (1.4-2.9 g/kg/day)	2-3 mg/kg/min (2.9-4.3 g/kg/day)

Phase of illness	Elaboration
Acute	Resuscitation phase when patient require vital organ support (sedation, mechanical ventilation, vasopressor, fluid resuscitation)
Stable	Patient is stable on or can be weaned from this vital support
Recovery	Patient who is mobilising

Blood glucose measurements should be performed using validated equipment (e.g. blood gas analysers). Hyperglycemia > 8mmol/L should be avoided in paediatric and neonatal intensive care units (PICU and NICU) patients due to increased morbidity and mortality. Repetitive blood glucose level > 10mmol/L should be treated with continuous insulin infusion. Repetitive and/or prolonged hypoglycemia ≤ 2.5mmol/L should be avoided in all ICU patients.

Potential complications and risks of carbohydrate infusion:

- Hyperglycaemia or hypoglycaemia.
- Glycosuria and potential osmotic diuresis.
- Cholestasis and/or hepatic steatosis (from prolonged high glucose concentration infusion).
- Enhanced very low density lipoportein (VLDL) triglycerides by the liver.
- Increased CO_2 production and minute ventilation.

5.3 Proteins

Proteins play vital roles in maintaining structural integrity and functional components of cells in the body. It is provided in PN solution to prevent catabolism and to achieve positive nitrogen balance in patients. In fact, the infusion of amino acid is recommended to be given to neonates from day 1 of life because the presence of amino acid in the blood stream can stimulate endogenous insulin secretion, hence reduce the frequency and severity of neonatal hyperglycaemia.

A minimum amino acid intake of 1.5 g/kg/day should be administered to both preterm and stable term neonates to achieve an anabolic state and to avoid a negative nitrogen balance. Higher intakes are needed to achieve physiological protein deposition. In preterm neonates, parenteral amino acid intakes above 3.5 g/kg/day should only be administered as part of clinical trials. The utilisation of amino acid supply requires sufficient energy intake. Energy provision of 30-40 kcal per 1 g amino acids is recommended.

Table 11. Parenteral amino acid supply considered adequate for stable patients[14]

Age	Protein Requirement
Preterm neonates Day 1 Day 2 onwards	 1.5 - 2.5 g/kg/day 2.5 - 3.5 g/kg/day
Term neonates	1.5 - 3.0 g/kg/day
2nd month – 3 years old	1 - 2.5 g/kg/day
3 - 18 years old	1 - 2.0 g/kg/day

Studies using high protein allotments of 4-6 g/kg/day have been associated with adverse effects such as azotemia, metabolic acidosis and neurodevelopmental abnormalities.[13]

Table 12. Individual amino acid requirements[14]

Amino acid	Requirement (mg/kg/day)
Tyrosine	74
Methionine + cysteine	47
Threonine	38
Lysine	105

Glutamine should not be supplemented additionally in neonates and children up to age of 2 years old. For taurine, there is no firm recommendation upon lower or upper limit, although it should be part of amino acid solution for neonates and children. Arginine may be used for prevention of NEC in preterm neonates.

Protein is administered as a solution of amino acids. 1g of protein yields 4 kcal of energy. Vaminolact® contains amino acids composition similar to human breastmilk.

Table 13. Relative concentrations of amino acids in Vaminolact® and human milk

Amino acid	Content (g/100g)	
	Human Breast Milk	Vaminolact®
Alanine	4.7	9.7
Arginine	4.6	6.3
Aspartic Acid	10.1	6.3
Cysteine	1.6	1.5
Glutamic Acid	18.1	10.9
Glycine	3	3.2
Histidine	3	3.2
Isoleucine	4.8	4.8
Leucine	10.4	10.8
Lysine	8.1	8.6
Methionine	1.9	2
Phenylalanine	4.1	4.2

Table 13 (con't). Relative concentrations of amino acids in Vaminolact® and human milk

Amino acid	Content (g/100g)	
	Human Breast Milk	Vaminolact®
Proline	8.5	8.6
Serine	5.5	5.8
Taurine	0.5	0.5
Threonine	5.3	5.5
Tryptophan	2.2	2
Tyrosine	3.9	0.8
Valine	5.4	5.5

Potential complications and risks of protein infusions:

- Acidosis
- Elevated blood urea nitrogen(BUN)
- Hyperammonaemia
- Cholestasis with prolonged administration

5.4 Lipids

Lipid emulsions are the major source of non-protein calories in the PN solution. The presence of lipid emulsions in PN solution improves the Non-Protein Calorie to Nitrogen Ratio (NPC:N) of the PN regimen, allowing protein to be utilised efficiently for anabolic processes, hence improving net nitrogen balance in the body. The inclusion of lipids in PN regimen also enable less carbohydrate to be given and thus decreases carbon dioxide production from excessive concentration of carbohydrates. Lipid intake of 25 - 50% of non-protein calories is recommended in fully parenterally fed patients.

Lipids contain polyunsaturated fatty acids such as linoleic acid and alpha linolenic acid which are essential components of neurodevelopment. In preterm neonates, lipid emulsions can be started immediately after birth and no later than on day two of life. In children, parenteral lipid intake should be limited to a maximum of 3 g/kg/day.

Table 14. Lipid requirements according to age[12,21]

Age	Initial (g/kg body weight/day)	Daily Increase (g/kg body weight/day)	Maximum (g/kg body weight/day)
Preterm neonates	0.5-1	0.5-1	3-4
Term neonates & children	1	0.5-1	3-4
Critically ill children	1	0.5-1	2-4

Table 14 shows the lipid requirements according to age. It is recommended to monitor patients' triglyceride (TG) level and the infusion rate of Intravenous Fat Emulsion (IVFE) should not exceed 0.125 g/kg/hour. Checking serum triglyceride levels may be considered within approximately 1 - 2 days after initiation or adjustment of lipid infusion.

Maximum amount of lipid that can be given safely is currently not known with certainty.

In preterm neonates, lipid given should not exceed 4 g/kg/day with linoleic acid requirement at 0.25 g/kg/day. In term neonates, lipid given should not exceed 4 g/kg/day with linoleic acid requirement at 0.1 g/kg/day. Fat oxidation for term neonates is 4 g/kg/day and for preterm neonates is 3 g/kg/day. In children, lipid given should not exceed 3 g/kg/day with linoleic acid requirement at 0.1 g/kg/day.

In patients with severe unexplained thrombocytopenia TG concentration should be monitored and reduction of lipid dosage may be considered. Reduction of dosage of IVFE can be considered if serum or plasma TG > 3mmol/L (265 mg/DL) in neonates and > 4.5 mmo/L in older children.

Potential complications and risks of lipid infusions:

- Hypertriglyceridemia in preterm neonate with physiologic jaundice and hyperbilirubinemia (> 18mg/dL) is associated with kernicterus.
- Potential risk of kernicterus at low levels of unconjugated bilirubin due to displacement of bilirubin from albumin binding sites by free fatty acids. As a general rule, lipids should not be increased beyond 0.5 g/kg/day until bilirubin is below threshold for phototherapy.
- Increased risk of exacerbation of chronic lung disease.
- Exacerbation of persistent pulmonary hypertension.
- Lipid overload syndrome with coagulopathy and liver failure.
- Hypersensitivity reaction (chills, fever, cyanosis, rash, nausea, vomiting).
- The clinical consequences associated with hypertriglyceridemia in neonates include increased risk of pancreatitis, immunosuppression and altered pulmonary haemodynamic.

Table 15. Composition of Intralipid® 20%, SMOFlipid® 20%, Lipofundin® 20% and Lipidem® 20% per 1000mL

Contents	Intralipid® 20%	SMOFlipid® 20%	Lipofundin® 20% MCT/LCT	Lipidem® 20% (Above 2 years)
Soybean oil (g)	200	60	100	80
Omega-3-acid triglycerides	-	-	-	20
Medium chain triglycerides	-	60	100	100
Olive oil	-	50	-	-
Fish oil, rich in omega-3-acids	-	30	-	-
Energy content (kcal)	2000	2000	1908	1910
Osmolarity (mOsm/L)	350	380	380	410

Generally, 1 g of fat yields 9 kcal of energy. Lipid emulsion preparation can be provided by a variety of product options such as Intralipid®, Lipofundin®, SMOFlipid® and Lipidem®. Table 15 below shows the composition comparison of the lipid sources that can be found in the market. Lipid emulsion is isotonic to human blood and thus when infused as one of the components in PN solution, it can reduce osmolarity of the overall solution and minimise the risk of thrombophlebitis. Standard 20% lipid emulsion contains a lower ratio of phospholipid emulsifier/ triglycerides than standard 10% lipid emulsion, and should preferably be used for intravenous PN to decrease the risk of hyperlipidemia. Direct exposure to ultraviolet rays especially during phototherapy, can cause the formation of harmful hyperoxides in the lipid emulsion.

To ensure the safety and effective use of lipids in PN, the following recommendations should be adhered to during lipid administration in neonates:

- Lipids should be infused over 24 hours to improve lipid clearance. Premature and term neonates have low lipoprotein lipase activity compared to adults. Hence, their fats clearance are less efficient.
- Vitamin E supplementation as an antioxidant. Lipid metabolism results in lipid peroxidation which leads to free radical formation. Free radicals can damage cell membranes during vitamin E deficiency.
- Lipid emulsions should be infused in light protective tubing.

5.5 Electrolytes

Electrolytes requirements are shown in the tables below. There are limitations to amount of calcium and phosphate that can be supplied in PN. Calcium and phosphate are able to form precipitate depending on the amounts added into the PN solution. One method of avoiding the risk of calcium-phosphate precipitation is to use organic phosphate and calcium salts. Another factor that can affect calcium and phosphate compatibility is the order in which calcium and phosphate are added. Phosphate is generally added first, while calcium is added near the end of the compounding sequence. Acidic solutions packaged in glass vial, such as calcium gluconate are contaminated with aluminum and should not be used in PN. It is not recommended to routinely add magnesium in the PN for neonates whose mothers have received therapeutic dose of magnesium (e.g. for tocolysis or as a prophylaxis).

5.5.1. Electrolytes Requirement in Neonatal Period

Phase I Transition phase

Table 16. Sodium and potassium requirements in neonates during transition phase[10]

Electrolytes	D1	D2	D3	D4	D5
Na^+ (mmol/kg/day)					
• Term neonate	0-2	0-2	0-2	1-3	1-3
• Preterm neonate > 1500g	0-2 (3)	0-2 (3)	0-3	2-5	2-5
• Preterm neonate <1500g	0-2 (3)	0-2 (3)	0-5 (7)	2-5 (7)	2-5 (7)
K^+ (mmol/kg/day)	0-3	0-3	0-3	2-3	2-3
Cl^- (mmol/kg/day)	0-3	0-3	0-3	2-5	2-5

Value of Na^+ in ( ) denotes the usual maximum Na^+ requirement during transition phase.

Phase II: Intermediate phase

Table 17. Sodium and potassium requirements in neonates during intermediate phase[10]

Neonates Category	Na^+ (mmol/kg/ day)	K^+ (mmol/kg/ day)	Cl^- (mmol/kg/ day)
Term neonate	2-3	1-3	2-3
Preterm neonate > 1500g	2-5	1-3	2-5
Preterm neonate < 1500g	2-5 (7)	1-3	2-5

Value of Na^+ in ( ) denotes the usual maximum Na^+ requirement during intermediate phase.

Phase III: Stable growth

Table 18. Sodium and potassium requirements in neonates during stable growth[10]

Neonates Category	Na^+ (mmol/kg/ day)	K^+ (mmol/kg/ day)	Cl^- (mmol/kg/ day)
Term neonate	2-3	1.5-3	2-3
Preterm neonate > 1500g	3-5	1-3	3-5
Preterm neonate < 1500g	3-5 (7)	2-5	3-5

Value of Na^+ in ( ) denotes the usual maximum Na^+ requirement during stable growth..

5.5.2. Electrolytes Requirement in children and infant beyond neonatal period

Table 19 summarises the sodium and potassium requirements while Table 20 shows the calcium, phosphate and magnesium requirements for paediatrics beyond neonatal stage.

Table 19. Sodium and potassium requirements in children and infant beyond neonatal period[10]

Age	Na^+ (mmol/kg/day)	K^+ (mmol/kg/day)	Cl^- (mmol/kg/day)
< 1 year old	2-3	1-3	2-4
1 – 2 years old	1-3	1-3	2-4
3 – 5 years old	1-3	1-3	2-4
6 – 12 years old	1-3	1-3	2-4
13 – 18 years old	1-3	1-3	2-4

Phosphate retention is related to bone mineralization, lean body mass accretion and protein retention.
Within physiological limits for compounding of PN the previously introduced equation for estimation of the Ca:P ratio in PN:

P intake (mmol)= [calcium intake (mmol/kg)/1.67] + [protein accretion (g)*0.3]

- Ideal Ca:P ratio seems close to 1 (0.8-1.2)
- In early PN when calcium and phosphorus intakes are low, protein and energy are optimised; recommended to use a molar Ca:P ratio below 1 (0.8-1.0)

To reduce the incidence of postnatal hypercalcemia and hypophosphatemia

Factors that can affect calcium and phosphate compatibility are:

- pH
- Temperature
- Presence of light
- Concentration of calcium and phosphate
- Amino acid concentration
- Calcium salt
- Presence of lipid

Table 20. Calcium, phosphate and magnesium requirements in paediatric patients[13]

Age	Ca^{2+} (mmol/kg/day)	PO_4^{3-} (mmol/kg/day)	Mg^{2+} (mmol/kg/day)
Preterm neonates during first day of life	0.8-2.0	1.0-2.0	0.1-0.2
Growing premature	1.6-3.5	1.6-3.5	0.2-0.3
0-6 months	0.8-1.5	0.7-1.3	0.1-0.2
7-12 months	0.5	0.5	0.15
1-18 years old	0.25-0.4	0.2-0.7	0.1

5.6 Vitamins

Vitamins are essential and should be an integral part of PN whenever PN is administered. However, the vitamins requirement of neonates and older children has not been extensively studied. Whenever possible, water and lipid soluble vitamins should be added to the lipid emulsion or a mixture containing lipids to increase vitamin stability. Table 21 below shows the estimation of vitamins intake in preterm neonates, term neonates, children and adolescent.

Table 21. Vitamins requirement in paediatric patients[15]

Vitamins (Water and lipid soluble)	Preterm neonates	Term neonates - 12 months	Children and adolescents (1-18 years)
Vitamin A	700-1500 IU/kg/d (227-455 µg/kg/d)	150-300 µg/kg/d or 2300 IU/d (697 µg/d)	150 µg/d
Vitamin D	200-1000 IU/d or 80-400 IU/kg/d	400 IU/d or 40-150 IU/kg/d	400-600 IU/d
Vitamin E	2.8-3.5 mg/kg/d or 2.8-3.5 IU/kg/d	2.8-3.5 mg/kg/d or 2.8-3.5 IU/kg/d	11 mg/d or 11 IU/d
Vitamin K	10 µg/kg/d	2.8-3.5 mg/kg/d or 2.8-3.5 IU/kg/d	200 µg/d

Table 21 (con't) . Vitamins requirement in paediatric patients[15]

Vitamins (Water and lipid soluble)	Preterm neonates	Term neonates - 12 months	Children and adolescents (1-18 years)
Vitamin C	15-25 mg/kg/d	15-25 mg/kg/d	80 mg/d
Thiamine	0.35-0.50 mg/kg/d	0.35-0.50 mg/kg/d	1.2mg/d
Riboflavin	0.15-0.2 mg/kg/d	0.15-0.2 mg/kg/d	1.4mg/d
Pyridoxine	0.15-0.2 mg/kg/d	0.15-0.2 mg/kg/d	1 mg/d
Niacin	4-6.8 mg/d	4-6.8 mg/d	17 mg/d
Vitamin B12	0.3 µg/kg/d	0.3 µg/kg/d	1 µg/d
Pantothenic Acid	2.5 mg/kg/d	2.5 mg/kg/d	5 mg/d
Biotin	5-8 µg/kg/d	5-8 µg/kg/d	20 µg/d
Folic Acid	56 mg/kg/d	56 mg/kg/d	140 mg/d

5.7 Trace Elements

Trace elements are important micronutrients required in vital body functions such as the metabolism of energy, protein, carbohydrate, lipid, nucleic acid and some of these trace elements are also essential for tissue accretion. Table 22 below shows the requirement of trace elements in preterm neonates, term neonates and children.

Table 22. Trace elements requirement in paediatric patients[16]

Trace Elements	Recommended Daily Requirements	Content in 1ml Peditrace
Zinc	• Preterm neonates : 400-500 µg/kg/d • Term neonates to 3 months : 250 µg/kg/d • 3-12 months : 100 µg/kg/d • > 12months : 50 µg/kg/d • Max: 5 mg/d	250 µg
Copper	• Preterm neonates : 40 µg/kg/d • Term neonates and children: 20 µg/kg/d • Max: 0.5 mg/d	20 µg
Fluoride	-	57 µg

Table 22 (con't). Trace elements requirement in paediatric patients[16]

Trace Elements	Recommended Daily Requirements	Content in 1ml Peditrace
Iodide	• Preterm neonates: 1-10 µg/kg/d • Term neonates and children: at least 1 µg/kg/d	1 µg
Selenium	• Preterm neonates : 7 µg/kg/d • Term neonates and children: 2-3 µg/kg/d • Max : 100 µg/kg/d	2 µg
Iron	• Preterm neonates: 200-250 µg/kg/d • Term neonates and children: 50-100 µg/kg/d	-
Molybdenum	• Preterm neonates: 1 µg/kg/d • Term neonates and children: 0.25 µg/kg/d • Max: 5 µg/kg/d	-
Chromium	• Daily intake: 0.2 µg/kg/d for term neonates and children • Max : 5 µg/kg/d	-

6.0 Monitoring

PN administration requires careful clinical and laboratory monitoring to avoid complications such as line-related sepsis, metabolic and mechanical complications. Through careful monitoring, complications can be minimised without diminishing the overall benefit of PN.

Careful monitoring of infusion line such as leakage and incorrect infusion rate due to problem arise from infusion pump errors is important. PN solutions with osmolality ≤ 900 mOsm/L can be administered peripherally for short term use provided that close monitoring of the IV site for any extravasation/ phlebitis is undertaken.[17]

For long term PN administration, measurement of trace elements and vitamins, at 6-monthly interval is recommended. Bone mineral density assessment is recommended at yearly interval.[7]

Table 23 shows the recommended laboratory and clinical monitoring parameters for patients on PN.

Table 23. Recommended laboratory and clinical monitoring [7,17,18,19]

Parameters	Unstable Patients	Stable Patients
Full Blood Count	Daily	2-3 times/week
Renal Profile	Daily or as needed	Once or twice a week
Ca^{2+}, PO_4^{3-}, Mg^{2+}	Twice weekly or as needed	Once weekly
Liver Function Test	For long term PN (>2 weeks duration) as needed	Once weekly or fortnightly
Blood glucose	4-6 hourly	Once or twice a day
Serum Triglyceride	24 hours after each increase	Once weekly unless complications arise
Weight	Once weekly	
Input/Output	Daily & adjusted as required	

7.0 Complications

Complications may arise during PN supplementation and can be grouped as follows:

- Stability of the PN solutions and Drug-PN interactions
- CVC-related complications
- Metabolic bone disease
- Hepatobiliary complications
- PN effects on growth parameters
- Metabolic & Nutritional complications

7.1 Stability of the PN Solutions and Drug-PN Interactions

7.1.1. Compatibility[7,20]

- Admixture formulation for preparing PN solution should be validated whenever possible by a licensed manufacturer or suitably qualified institution.
- The formulation detailing permissible limits for additions of electrolytes and other additives should be sought from the suppliers that are supplying the raw materials.
- Alternative ingredients are not recommended to be substituted without expert advice or repeat validation.
- Organic bound form of phosphate is preferred over inorganic phosphate to prevent the risk of calcium-phosphate precipitation.

(con't)

7.1.1. Compatibility[7,20]

- If any inorganic phosphate to be used in the formulation, strict order of mixing PN components must be followed and maximum calcium-phosphate concentration must be taken into consideration. However, occasional precipitates may still occur due to various factors.
- The administration of Y-site lipids together with '2 in 1' PN admixtures via the same infusion line is feasible if proven to be compatible based on the validation by manufacturer or the lipid may be infused through an alternative line.
- A terminal filter should be used when administering PN.
- The standard filter size for '2 in 1' PN admixtures without lipid is 0.2 micron whereas a 1.2 micron filter should be used for the administration of lipids emulsion and '3 in 1' PN solutions.

7.1.2. Drug Interactions[7,20]

- Whenever possible, avoid mixing medications with PN unless validated by the manufacturer or accredited laboratory.
- Medications known to affect plasma protein binding of bilirubin should be avoided in parenterally fed newborn patients with severe hyperbilirubinaemia.

7.1.3. Peroxidation, Light Protection and Vitamin Stability[7,20]

- It is recommended to use multi-layer bags which are impermeable to oxygen for PN administration.
- Light protection is recommended for both PN bags and administration sets.

7.1.4. Osmolarity[7,20]

- The recommended delivery site for PN is via a central line. However, peripheral PN can also be given for short periods.
- The osmolarity of peripheral PN solution should be kept at less than 900 mOsmol/L.

7.2 CVC-Related Complications[7,20]

7.2.1. Catheter-Related Infections

- PN solution should be prepared aseptically in a suitable environment according to Good Preparation Practice (GPP).
- The infusion sets and extensions should be used no more than 72 hours and changed as recommended by the manufacturers.
- Lipid infusion sets need to be changed 24 hours after usage or as recommended by the manufacturers.
- PN solutions that are disconnected from the catheter should be discarded.
- If catheter-related sepsis (CRS) is suspected, a paired quantitative blood cultures taken simultaneously from both the CVC and a peripheral vein should be obtained before the start of antibiotic therapy.
- Empirical intravenous antibiotics that covers Gram-positive coagulase-negative or positive staphylococci and Gram-negative bacilli should be commenced promptly whenever CRS is suspected.
- Once the infecting microorganism has been identified, a narrower spectrum antibiotic therapy should be given and duration of therapy for CRS with a retained catheter is generally 10-14 days, assuming clinical and microbiological response within 48-72 hours and no evidence of complications.
- CVC is recommended to be removed if clinical deterioration or persisting or relapsing bacteremia, presence of suppurative complications or positive blood cultures after 72 hours of appropriate antibiotics.

7.2.2. Occlusion

- Occlusion of the CVC can be originated from:
  I. Within the CVC lumen due to blood, drug or PN fluid precipitate.
  II. In the vein due to clot or fibrin sheath.
  III. External to the CVC due to the tip resting against a vein wall or due to external compression such as clavicle, or patient positioning.

7.2.2.1. Thrombotic Occlusion and CVC-Related Thrombosis

- CVC-related thrombosis usually involve the catheter tip, the length of the catheter, or the catheterised vessel.
- Even though most of the incidence is asymptomatic, but the initial symptoms might include difficulty in flushing or obtaining blood from the catheter.
- Symptoms of CVT include head and neck swelling, pleural effusion, chemosis plethora, and lower limb edema, while symptoms of Pulmonary Embolism (PE) include dyspnoea, stridor, hoarse cry, airway occlusion, and chest pain in older children.
- CVT in children can lead to loss of subsequent intravenous access, recurrent thrombosis, PE, post thrombotic syndrome and death.
- Fibrinolytics agents are the drug of choice for the treatment of thrombotic catheter occlusion. The recommended drug is Tissue plasminogen activator (tPA, alteplase) but urokinase and recombinant urokinase (rUK) can also be used.
- Antithrombotic medication is recommended for the treatment of acute and symptomatic catheter-related thrombosis. If the catheter is in-situ, anticoagulation, including low-molecular-weight heparin (LMWH) subcutaneously or unfractionated heparin (UFH) intravenously, is the main initial therapy. If major vessel occlusion is involved and compromising the organ and limbs, thrombolytic therapy is recommended.
- Children that are on long term PN, thromboprophylaxis with vitamin K antagonists has been suggested.

7.2.3. Extravasation, Breakage and Migration

- Extravasation is defined as the leakage of infusate from a vein into the subcutaneous space.
- It can be life-threatening which includes pleural or pericardial effusion and cardiac tamponade.
- Catheters that are positioned at the loop of acute angles are at risk of fracture. The signs include local swelling, pain, or skin site leakage on injection.
- Migration of the catheter tip can also happen to locations such as the internal jugular vein or contralateral brachiocephalic vein.
- It is important to make sure that the catheter tip is positioned properly.
- If catheter breakage or fluid extravasation is suspected, immediate investigation should be implemented in order to prevent the occurrence of significant morbidity.
- It is recommended to take appropriate measures to secure the catheter in place and educate users on the correct maintenance and safety of the catheter.

7.3 Metabolic or Nutritional Complications

7.3.1. Re-feeding Syndrome[7,20]

- Feeding to a malnourished child may cause refeeding syndrome which is principally associated with hypophosphataemia, hypomagnesaemia, hypokalaemia, vitamin deficiency and fluid retention.
- Refeeding syndrome could be life-threatening, thus PN regimen must be formulated wisely and monitored closely.

Several conditions as stated below must be taken into consideration in the initial phase of re-nutrition of severely malnourished neonates and children:

I. Prevention of water and sodium overload:
-Water and sodium intake should be reduced. However, this depends on the hydration status of the malnourished neonates and children.

-Fluid monitoring is essential to detect early fluid retention which could be observed by patients excessive weight gain.
Maintaining stable weight is highly recommended or may try to achieve weight loss during the first 2-3 days of parenteral re-nutrition.
-Slow infusion of albumin at 1 g/kg, twice a day can be given if necessary for preserving the oncotic pressure.
-Insensible losses or losses from the gastrointestinal tract, intraperitoneal or intestinal fluid retention should be monitored.

II. Carbohydrate intake:
-Continuous glucose infusion provided should be tailored to the age of the patient and the rate may be at least equal to the glucose production rate.

III. Potassium repletion:
-Potassium correction should be done progressively with monitoring of renal and cardiac function as it can be fatal if the deficiency is corrected too rapidly. Excessive potassium intake may cause hyperkalaemia and cardiac arrhythmia.

IV. Phosphorus repletion:
-Phosphorus depletion should be corrected progressively with monitoring of neurological status and renal function.
-Minimum intake of 0.5 mmol/kg/day is recommended and proportionally increased according to the total protein energy intake up to 1.0 mmol/ kg/day.
-It is mandatory for daily monitoring of phosphoraemia and phosphaturia by aiming at a limited phosphaturia.

V. Protein and energy intake:
-An intake of 0.5-1 g/kg of parenteral amino acids or oral peptide is recommended in the initial phase of re-nutrition as excessive nitrogen intake may cause hyperammonaemia/ metabolic acidosis.

-The protein energy deficiency should be corrected gradually during the days following the initial period of stress.
-It is important to provide both nitrogen and calories simultaneously and in the correct ratio.
-In children and adolescents the initiation energy required is approximately 20 kcals/kg/day then gradually increase the energy.

7.3.2. Biochemical Imbalances[18,20]

- Monitoring the biochemistry is important to allow adjustment of PN when imbalance occur.

I. Hyperglycemia and hypoglycemia
-Blood glucose level of > 8mmol/L is considered as hyperglycemia.
-Blood glucose level of ≤ 2.5mmol/L is considered as hypoglycemia.

II. Hypernatraemia and hyponatraemia
-Hypernatraemia occurs when serum sodium level is > 145mmol/L.
-Hyponatraemia occurs when serum sodium level is < 135mmol/L.

III. Hyperkalemia and hypokalemia
-Hyperkalemia occurs when serum potassium level is > 6 mmol/L or if ECG changes have developed.
-Hypokalemia occurs when serum potassium level is < 3.5mmol/L.

IV. Hypercalcaemia and hypocalcaemia
-Hypercalcaemia occurs when total serum calcium level is > 2.75 mmol/L
-Hypocalcaemia occurs when total serum calcium level is < 1.75mmol/L.

V. Hyperphosphataemia and hypophosphataemia
-Level of phosphate for hyperphosphataemia and hypophosphataemia is dependent of the patient age.

VI. Hypermagnesaemia and hypomagnesaemia
-Hypermagnesaemia occurs when serum magnesium level is > 1.25 mmol/L.
-Hypomagnesaemia occurs when serum magnesium level is ≤ 0.65mmol/L.

VII. Severe metabolic acidosis
-Occurs when the pH < 7.2 with base deficit > 10mmol/L or bicarbonates < 12mmol/L .
-It may be induced by high accumulation of chloride in PN.
-Hence, the use of chloride free sodium and potassium should be considered to reduce the risk of hyperchloraemia and metabolic acidosis

7.3.3. Metabolic Bone Disease[7,20]

- Little data of PN related metabolic bone disease (MBD) exists in children, although its occurrence has been reported in children with long term PN.
- Therefore, regular measurements are recommended to be performed on urinary calcium, plasma calcium, phosphorus, parathyroid hormone, vitamin D concentrations and serum alkaline phosphatase particularly for children on long term PN.
- Risk of contamination with aluminium in PN solutions should also be avoided and minimised.
- In order to prevent MBD, regular assessment of bone mineralisation should be performed.

7.3.4. Hepatobiliary Complications of PN[7,20]

- Risk of developing liver disease can be due to patient related condition such as patient on prolonged PN, absence of oral feeding, short bowel syndrome as well as recurrent septic episodes.

- However, PN may also aggravate liver injury due to excess of total energy delivered that induces liver lesions, excessive or inadequate amino acid supply, continuous PN infusion or excessive glucose intake which may lead to hyper-insulinism and subsequent steatosis, inadequate lipid supply with excessive delivery of fat and subsequent lipoperoxidation as well as the phytosterols contain in the lipid emulsion.
- Liver disease can be prevented by reducing both patient related and PN related risk factors as mentioned above by:

I. Providing maximal tolerated enteral nutrition despite of minimal residual gut function.

II. Introducing cyclical PN immediately.

III. Treat intraluminal bacterial overgrowth by giving metronidazole or by performing venting enterostomy or tapering enteroplasty.

IV. May reduce or stop IV lipids temporarily if conjugated bilirubin progressively increases with no other explanation.

V. Commencing ursodeoxycholic acid at 10 to 30 mg/kg/day if the transaminases, alkaline phosphatase or conjugated bilirubin are increasing.

VI. Early referral and assessment from an experienced paediatric liver and intestinal transplant centre is highly recommended if the neonates/children have poor prognosis or if on PN for 3 months and serum bilirubin 50 µmol/L, platelet count less than 100, PT more than 15 seconds, PTT more than 40 seconds or hepatic fibrosis.

7.3.5. Growth Retardation[7,20]

- Infant or children on prolonged PN must receive adequate nutrition not only to meet its basic metabolic requirements but also to allow for normal growth.
- Therefore, paediatric patients on long term PN require regular monitoring of growth and body composition to prevent abnormalities in growth and nutritional status in later childhood.

8.0 Transitioning PN to EN & Discontinuing PN

While transitioning from PN to EN, calorie intake and glycaemic control should be optimised. Total fluids intake should be maintained while weaning off PN and increasing EN.

In preterm neonates, once enteral nutrition volumes are increased beyond trophic/minimal amounts (> 30 ml/kg/day) and are clinically considered to be tolerated, their contribution to nutritional intake should be considered when calculating PN requirements[18].

- As the enteral nutrition volumes increase, PN should be reduced accordingly without compromising nutritional intake.
- The lipid infusion should be reduced accordingly with advancing enteral nutrition to ensure maximum lipid tolerance is not exceeded.
- Both the lipid infusion and aqueous PN infusion should be continued until the neonate tolerates at least 120 ml/kg/day enteral nutrition.
- The total fluid volume provided from parenteral and enteral nutrition may be increased above 150 ml/kg/day if required to meet fluid and nutrient requirements once there are no contraindications.

In older children, practical considerations when weaning PN include the following[18]:

- There should be a gradual transition from PN once a clinical decision has been made to commence enteral nutrition.
- Full PN volumes should continue until at least 25% of nutritional requirements are met from enteral or oral nutrition.
- When reducing PN, ensure that aqueous and lipid solutions are reduced in correct proportion to each other.

9.0 Appendix

Calculation of PN Osmolarity

1. Osmolarity (mOsm/L) = [CHO(g)x5] + [AA(g)x10] + [Fat(g)x0.71] + [Elec(mEq)x1]
   Volume (L)

CHO: Carbohydrate
AA : Amino Acids
Elec : Electrolytes

Ref: Mirtallo J, Canada T, Johnson D et al.Task force for the revision of safe practices for parenteral nutrition. 2004. Safe Practices for Parenteral Nutrition. Journal of Parenteral and Enteral Nutrition.28(6):S39-S70.

2. Osmolarity (mOsm/L) = Carbo(g)x5 + AA(g)x10 + Cations*(mEq)x2@4
Volume(L)

*Cations with mono-valens (x2)
*Cations with di-valens (x4)

Ref: Rollins CJ. Peripheral Parenteral Nutrition. M.V.I. Newslines (sponsored by Astrazeneca LP)

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